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Screening of Urine Samples by Flow Cytometry Reduces the Need for Culture[∇]

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Urine samples constitute a large proportion of samples tested in clinical microbiology laboratories. Culturing of the samples is fairly time- and labor-consuming, and most of the samples will yield no growth or insignificant growth. We analyzed the feasibility of the flow cytometry-based UF-500i instrument (Sysmex, Japan) to screen out urine samples with no growth or insignificant growth and reduce the number of samples to be cultured. A total of 1,094 urine specimens sent to our laboratory for culture during 4 months in the spring of 2009 in Lahti, Finland, were included in the study. After culture, all samples were analyzed with the Sysmex UF-500i for bacterial and leukocyte (white blood cell [WBC]) counts. Youden index and closest (0,1) methods were used to determine the cutoff values for bacterial and WBC counts in culture-positive and -negative groups. By flow cytometry, samples considered positive for UTI in culture had bacterial and WBC values that were significantly higher than those for samples considered negative. The flow cytometric screening worked best when both bacterial counts and WBC counts were used with age- and gender-specific cutoff values for all patient groups, excluding patients with urological disease or anomaly. By use of these cutoff values, 5/167 (3.0%) of culture-positive samples were missed by UF-500i and the percentage of samples that did not need to be cultured was 64.5%. Use of the UF-500i instrument is a reliable method for screening out a major part of the UTI-negative samples, significantly diminishing the amount of work required in the microbiology laboratory.

Urinary tract infections (UTIs) are among the most common infections treated by community health care centers and hospitals (5, 6, 13, 19, 24). In Finland, urinary tract infections account for approximately 6% of all infectious disease diagnoses in primary care (20) and urine samples constitute a large proportion of the samples tested in clinical microbiology laboratories (13, 18, 24). The gold standard for UTI diagnosis is bacterial culture, which is based on bacterial counts and identification. Culturing of the samples is fairly time- and labor-consuming, and most of the samples yield no growth or insignificant growth (10, 15, 22, 24). In order to improve the efficiency of handling of the urine samples, methods for screening out the culture-negative samples from the culture-positive samples have been developed. Chemical screening with strips for nitrite, pH, leukocytes, erythrocytes, albumin, and glucose is widely used (17, 18, 22, 23), but a meta-analysis of the literature (4) has shown that the method is insensitive and is suitable as a rule-out test only when both nitrite and leukocyte-esterase are negative. Cells, particles, and microorganisms in urine can be examined by microscopic-urine-sediment analysis, but this method is time-consuming, labor-intensive, and sensitive to interobserver variability (2, 7, 8, 10, 12, 21).

Pyuria with bacteria predicts bladder infection better than the presence of bacteria alone, and therefore, a screening method that detects both leukocytes and bacteria is favorable for the identification of patients with urinary tract infections (18). During the last 10 years, the use of flow cytometry-based analyzers that measure quantitatively both leukocytes and bacteria has been evaluated (2, 6, 8, 10–16, 21, 25). The studies done with the first-generation Sysmex instruments, UF-50 and UF-100, showed variable results concerning the suitability of this technology for screening purposes (3, 6, 15, 25). The second-generation Sysmex analyzers, UF-500i and UF-1000i, have a separate measurement channel for bacteria which improves the specificity for counting of bacterial organisms.

The aim of this study was to evaluate the feasibility of flow cytometry using a UF-500i instrument (Sysmex Corporation, Japan) in routine diagnosis of UTI. We sought to develop a screening strategy in which as few samples as possible needed to be cultured, while maintaining a low level of false negatives and a high negative predictive value.

MATERIALS AND METHODS

For this study, 1,094/9,502 (11.5%) urine samples from hospitalized patients and outpatients, submitted for culture during 4 months in the spring of 2009, were analyzed with the Sysmex UF-500i instrument after culture. A great number of samples were excluded from the study because the study protocol could not be followed, mostly due to storage time being exceeded. Also, a very small number of samples, less than 1%, were discarded because of visible blood, mucus, or fluorescent dyes to prevent blockage of the instrument or interference during the measurement. Of the eligible samples, 386 (35.3%) were from male patients (0 to 92 years of age) and 708 (64.7%) from female patients (0 to 99 years of age).

Samples were collected in nonpreservative tubes and were transported at cold temperatures and stored in a refrigerator when they could be analyzed within 4 h. Samples were collected in preservative tubes (Vacutainer Plus C&S boric acid; BD, Franklin Lakes, NJ) and were transported and stored at room temperature

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TABLE 1. Medians and ranges of bacterial numbers and white blood cell counts (by the UF-500i device) and *P* values

Method/cell type	Cells/μl for urine sample by test result[a]			*P* value[b]
	Negative		Positive	
	No growth	Growth insignificant[c]		
Standard culture[d]				
Bacteria	9.1 (0–10,116)	58.8 (1–61,957)	10,485 (2–87,096)	<0.0001
WBCs[e]	2.4 (0–3,858)	5.5 (0–43,144)	198.9 (1–48,202)	<0.0001
Sensitized culture[f]				
Bacteria	2.7 (0–142)	15.6 (0–42,805)	74.5 (2–22,846)	<0.001
WBCs	2 (0–373)	3.5 (0–2,560)	12.8 (1–689)	0.025

[a] Median values (ranges in parentheses).
[b] *P* value corresponding to the positive group compared to the combined negative groups.
[c] See Materials and Methods.
[d] Inoculation with a 1-μl loop.
[e] WBCs, white blood cells.
[f] Inoculation with a 10-μl loop

when they could be analyzed within 4 to 8 h. All samples were cultured within 24 h.

The samples were directly aspirated to the flow cytometry instrument (UF-500i flow cytometer; Sysmex, Japan) without any prior preparation. After the aspiration, the instrument dilutes a urine sample into two different reaction volumes. In the sediment reaction, all the nucleic acid-containing cells are stained using polymethine dye. In the bacterial reaction, only nucleic acids in bacteria are stained. The instrument utilizes flow cytometry by using a red semiconductor laser to detect the particles in the stained sample. Particle characterization and identification are based on detection of fluorescence, forward-scatter light, and side-scatter light. In this study, only bacterial and leukocyte (white blood cell [WBC]) counts were used for sample interpretation. Software version 00-04 for the UF-500i analyzer was used (corresponding to software version 00-15 for the UF-1000i analyzer). The instrument analyzes at most 60 samples per hour.

For culture, samples were inoculated using a 1-μl loop (standard culture) on nonselective chromogenic agar plates (CHROMagar Orientation agar; BD, Franklin Lakes, NJ) supporting the growth of UTI pathogens, and the results were interpreted according to the Finnish national guidelines (9). After 24 h of incubation at +37°C, cultures were quantified and bacteria identified. A sample was considered negative for a UTI if there was no growth or there was $\leq 10^3$/ml bacterial growth (interpreted as insignificant growth). A value of $>10^3$/ml bacterial growth was considered positive for a UTI if the patient had symptoms for a UTI, if the urine had stayed in the bladder for less than 4 h, or if the patient was male and had a catheter. In other cases, samples with $>10^4$/ml bacterial growth were considered positive for a UTI. If more than two organisms were isolated, the sample was reported as "mixed flora" without any further identification and a new sample was requested for verification. Samples from patients with urological disease or anomaly were inoculated using a 10-μl loop (sensitized culture) instead of the 1-μl loop (standard culture; see above). The patients with urological disease or anomaly were identified by request or diagnosis in the laboratory information system. For these samples, $>10^2$/ml bacterial growth was considered to correspond to significant bacteriuria if the patient had symptoms for UTI, if the urine had stayed in the bladder for less than 4 h, or if the patient was male and had a catheter. In other cases, $>10^3$/ml bacterial growth was considered a positive result for a UTI. Identification of the bacteria/yeasts was performed by using an automated instrument (Vitek 2; bioMérieux, Marcy l'Etoile, France) or conventional biochemical methods.

Statistical analysis was performed using SPSS 12.0.1 for Windows, with culture as the gold standard. For analysis, samples were divided into two groups: negative for UTI and positive for UTI by culture. The negative group consisted of samples for which no bacterial growth was detected and specimens with insignificant growth (the organism quantity was too low, the organism was nonpathogenic, or mixed growth was detected). The normality of the distributions of WBCs and bacteria were tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Statistical significance was evaluated by the Mann-Whitney test, and the level of significance was set to 0.05. Diagnostic accuracy of WBC and bacterial counts for UTIs was measured by the area under the receiver operating characteristic (ROC) curve (i.e., the area under the curve [AUC]). The Youden index [calculated as the maximum (Se + Sp − 1) value] and closest (0,1) {calculated as the minimum $[(1 - \mathrm{Se})^2 + (1 - \mathrm{Sp})^2]$ value} methods were used to estimate the best cutoff points to discriminate samples in the positive and negative groups.

RESULTS

Of the 1,094 samples, 184 (16.8%) were positive for UTI by culture. One hundred sixty-seven of the UTI-positive samples were detected by standard culture and 17 by sensitized culture. Bacterial strains observed in these samples were typical for UTI, with *Escherichia coli* (53.8%), *Enterococcus* spp. (14.1%), and *Klebsiella* spp. (10.6%) as the most prevalent species. Nine hundred ten samples were negative for UTI by culture. In 648 (71.2%) of these samples, there was no growth seen in urine culture, while in 262 samples (28.8%), growth was interpreted as insignificant. Among samples UTI negative by standard culture, group distributions of no-growth and insignificant-growth samples were 564 (72.2%) and 217 (27.8%). For sensitized-culture samples, the corresponding figures were 84 (65.1%) and 45 (34.9%), respectively.

Medians and ranges of bacterial and WBC counts for groups negative and positive for UTI by culture are shown in Table 1. The results indicate that with standard culture, samples positive for UTIs had significantly higher bacterial and WBC counts than samples negative for UTI. This was also the case with age- and gender-based subpopulations ($P < 0.001$; data not shown). With the sensitized culture, only differences between bacterial cell counts for positive and negative groups reached statistical significance ($P < 0.001$). However, for a subpopulation of male patients ($n = 121$), significant differences between the bacterial ($P = 0.001$) and WBC ($P = 0.047$) counts of the negative and positive groups were detected. For female patients ($n = 25$), there was no significant difference between either bacterial ($P = 0.129$) or WBC ($P = 0.243$) results for these groups.

ROC curve analyses showed that the discriminatory powers for both bacteria (AUC, 0.944) and WBCs (AUC, 0.902) for the standard-culture group were better than those for the sensitized-culture group (AUC for bacteria, 0.809; AUC for WBCs, 0.668). Even though the AUC values for the bacterial counts (contrary to WBC counts) in the sensitized-culture group were quite high, due to a low number of positive samples

TABLE 2. Outcome of screening with different cutoff value combinations (standard culture[a] only)

Patients and index[b]	Cutoff value (cells/μl) for:		No. of false negative samples/ UTI[c]-positive samples (%) missed by UF-500i[c]	Se[d]	Sp[e]	NPV[f]	Screened neg (%)[g]
	Bacteria	WBCs					
Total							
Youden index	405	16	11/167 (6.6)	0.934	0.823	0.983	69.0
Closest (0,1)	405	16	11/167 (6.6)	0.934	0.823	0.983	69.0
Children (0–15 yr)							
Youden index	41	17	0/13 (0.0)	1.000	0.783	1.000	70.3
Closest (0,1)	70	17	2/13 (15.4)	0.846	0.843	0.980	77.3
Adults							
16–65 yr							
Youden index	634	10	1/32 (3.1)	0.969	0.826	0.997	76.0
Closest (0,1)	146	10	1/32 (3.1)	0.969	0.749	0.996	68.9
>65 yr							
Youden index	399	16	6/122 (4.9)	0.951	0.775	0.976	57.2
Closest (0,1)	399	17	6/122 (4.9)	0.951	0.784	0.976	57.9
Males							
Youden index	42	10	1/31 (3.2)	0.968	0.812	0.995	72.1
Closest (0,1)	42	17	1/31 (3.2)	0.968	0.855	0.995	75.8
Females							
Total							
Youden index	758	16	8/136 (5.9)	0.941	0.821	0.982	66.9
Closest (0,1)	453	16	8/136 (5.9)	0.941	0.804	0.982	65.6
16–65 yr							
Youden index	634	10	0/28 (0.0)	1.000	0.833	1.000	75.5
Closest (0,1)	146	10	0/28 (0.0)	1.000	0.733	1.000	66.4
>65 yr							
Youden index	726	16	6/98 (6.1)	0.939	0.744	0.963	52.8
Closest (0,1)	726	17	6/98 (6.1)	0.939	0.740	0.964	52.7

[a] Inoculation with a 1-μl loop.
[b] The Youden index was calculated as the maximum (Se + Sp − 1). The closest (0,1) value was calculated as the minimum $[(1 - \text{Se})^2 + (1 - \text{Sp})^2]$.
[c] UTI, urinary tract infection.
[d] Se, sensitivity.
[e] Sp, specificity.
[f] NPV, negative predictive value.
[g] Screened neg, WBC and/or bacterial counts under the cutoff value.

in this group (17/146; 11.6%), the calculation of cutoff values (see the next paragraph) for different subpopulations was not considered feasible.

Both the Youden index and closest (0,1) methods were used to calculate the optimal cutoff values for all samples cultured with the standard method and also for different subpopulations to find out if there were differences due to age and gender (Table 2). The corresponding cutoff values based on these methods were close to each other, except for those for bacteria in adults 16 to 65 years of age and females 16 to 65 years of age, which had a considerably higher value with the Youden index method. However, since using this higher value did not increase the number of false negatives in these patient groups, we chose to use the Youden index in our analysis of all patient groups. The optimal cutoff values for bacteria differed greatly between different subpopulations, whereas for WBCs, they were much more consistent. The best performance of the rule-out strategy (few false negatives and a high negative predictive value) was achieved when both bacterial and WBC counts were used for screening. If either the bacterial or WBC count was above the suggested cutoff limits, the sample was interpreted as positive and cultured.

If one common cutoff value set had been used for all samples sent to the laboratory for standard culture, this would have resulted in 11 false-negative screening results (Table 2). However, if subpopulation-specific cutoff values are used, a better clinical performance of screening is achieved. Since the Youden index method gave nearly the same cutoff values for children and males, identical cutoff values were chosen for the two groups (Table 3). For females, the best performance was achieved by using the cutoff values originally established for females 16 to 65 years of age (630/μl for bacteria and 10/μl for WBCs; Table 2). By using these cutoff values, five false-negative samples (Table 4) were found in the whole standard culture group, representing 3.0% (5/167) of the UTI-positive samples and 0.5% (5/948) of the whole standard-culture group. The percentage of samples that did not need to be cultured was 64.5%.

DISCUSSION

In this study, we determined age- and gender-dependent cutoff values for flow cytometric screening of samples submitted for urine culture. By using this method, we were able to reduce the number of cultures significantly with only a small number of false-negative screening results. The method is applicable to all patient groups except for those such as patients with urological disease or anomaly or possibly immunocompromised patients, for which further verification is needed.

The urine samples we studied were from hospitalized pa-

TABLE 3. Combined (bacterial and WBC) optimal cutoff values for children and male and female patients (standard culture[a])

Group	Cutoff value (cells/μl) for:		No. of false-negative samples/UTI-positive samples (%) missed by UF-500i	Se[b]	Sp[c]	NPV[d]	Screened neg (%)[e]
	Bacteria	WBCs					
Children (0–15 yr)	40	17	0/13 (0)	1.000	0.783	1.000	70.3
Males (≥16 yr)	40	17	1/28 (3.6)	0.968	0.812	0.995	72.1
Females (≥16 yr)	630	10	4/126 (3.2)	0.968	0.755	0.989	60.5
Combined			5/167 (3.0)	0.970	0.777	0.992	64.5

[a] Inoculation with a 1-μl loop.
[b] Se, sensitivity.
[c] Sp, specificity.
[d] NPV, negative predictive value.
[e] Screened neg, WBC and/or bacterial counts under the cutoff value.

tients and outpatients, and patients were from all age groups. We excluded specimens with apparent interfering factors and specimens for which the study protocol could not be followed, e.g., those for which the time lag between sampling and analysis exceeded our criterion. Consequently, a great number of samples were discarded. However, the prevalence of UTIs in our study was 16.8%, and the distribution of causative agents was typical for UTIs. This is in good agreement with data from the literature. Thus, in our opinion, our study is representative of the heterogenic patient materials typically analyzed by clinical microbiological laboratories.

For a rule-out strategy, the cutoff point determination is a difficult task, as increasing test sensitivity decreases its specificity. ROC analysis is a commonly used method for determination of cutoff points at which optimal sensitivity and specificity are achieved for clinical use. Two methods, the Youden index and closest (0,1) methods, are both commonly used for identifying such cutoff points on the ROC curve (1). In our study, the cutoff values based on these methods were close to each other except for those for bacteria in adults 16 to 65 years of age and females 16 to 65 years of age, which were considerably higher with the Youden index method. However, since use of the higher values did not increase the number of false negatives in these patient groups, we chose to use the Youden index in our analysis of all patient groups.

The first-generation flow cytometry analyzers UF-50 and UF-100 have one measurement channel for detection of all particles, including bacteria. The identification algorithm is based on two measured signals, fluorescence and forward-scatter light. In these instruments, the detected number of bacteria is high due to the fact that other particles showing similar staining and size are counted as bacteria. Although the identification of bacteria is not very specific, the suitability of these first-generation instruments has been evaluated for UTI screening in many studies with various patient materials (3, 6, 10, 11, 14, 15, 25). In these studies, only one set of cutoff values has been used. For instance, Evans and coworkers (6) established one set of cutoff values for bacteria (3,000/μl) and leukocytes (111/μl) in their study, which consisted of 1,005 consecutive urine samples from hospital and general practice patients from all age groups. They reached a negative predictive value of 96% and sensitivity of 92%. They succeeded in reducing the number of urine samples requiring culture by 40% and concluded that the UF-100 device is suitable for screening out negative urine samples. However, Zaman and coworkers (25) found that the UF-100 device alone or combined with chemical screening was not suitable for screening, since both the negative predictive value (87.5%) and the sensitivity (84.2%) were less than 95%, with values of ≥95% considered to be acceptable for a rule-out strategy.

In second-generation analyzers UF-500i and UF-1000i, a dedicated measurement channel for bacteria counting was added. In this channel, only nucleic acids in bacteria are stained by fluorescent dye. The separate measurement channel improves the specificity of counting of bacteria. Furthermore, side-scattered light signal is detected both in sediment and in bacterial channels. This signal is used in algorithms to achieve more-specific identification of different cells. For these reasons, the second-generation analyzers seem more attractive for screening purposes than the earlier models. Manoni et al. (13) established cutoff values for bacteria (125/μl) and leukocytes (40/μl) by using a UF-1000i analyzer, which is basically identical to the instrument used in this study (UF-500i). However, their patient material came from adults only and their criterion of culture positivity (growth of 10^6/ml or more) was different from ours. By use of one set of cutoff values for screening, their test sensitivity was 97.0% and their negative predictive value was 98.0%. In our study, using one set of cutoff values would have resulted in a sensitivity slightly lower (Table 2) than the sensitivity with age- and gender-specific values. With age- and

TABLE 4. False-negative samples in the study population (standard culture[a])

Sample	Patient gender	Age (yr)	Bacteria/μl	WBCs/μl	Growth (bacteria/ml)	Isolate(s)
1	Male	60	14.6	2.1	10^3–10^4	*Klebsiella oxytoca*
2	Female	72	1.8	0.6	10^3–10^4	*Pseudomonas aeruginosa*
3	Female	82	64.3	5.9	10^4–10^5	*Enterobacter cloacae*
4	Female	71	78.2	3.9	10^4–10^5	*Escherichia coli*, *Citrobacter freundii*
5	Female	74	98.4	0.6	10^4–10^5	*Pseudomonas aeruginosa*

[a] Inoculation with a 1-μl loop.

gender-specific cutoff values (Table 3), only five false-negative samples (3.0%) were found, compared to 11 (6.6%) when using one set of cutoff values for all samples. The five false-negative samples all showed common Gram-negative UTI pathogens in culture (Table 4), and considering the borderline culture results and low WBC counts, they may represent colonization rather than UTI. Manoni and coworkers (in 2009) (13) also found a low number of false-negative screening results, but in contrast to our results, these were Gram-positive bacteria, fastidious Gram-negative bacteria, or *Candida* species. False-negative results with the Sysmex UF-100-analyzer have also been reported earlier (14, 25), especially for Gram-positive bacteria due to aggregation of bacterial cells.

The sensitivity of the screening test for UTIs is more important than the specificity (13). This is due to the fact that all samples positive in the screening test will be cultured, and therefore, false-positive results, as determined by culture, are not reported to the clinicians. In our study, 172 false-positive cases (172/948 [18.1%]; standard culture only) were observed. A majority of these false-positive samples had high leukocyte counts, showed growth of mixed flora, or had high quantities of particles counted as bacteria by the UF-500i device but no growth in culture. Some of the samples might have had non-viable bacteria, especially if antimicrobial therapy had been started before sampling. For a rule-out strategy, we reached a balance between an acceptable negative predictive value of 99.2% and reduction of urine culture corresponding to 64.5%.

To conclude, by using age- and gender-specific cutoff values, use of the UF-500i instrument is a reliable method for screening out a major part of the UTI-negative samples. For patients with urological disease or anomaly or possibly other patient groups such as immunocompromised patients, the method needs further validation. The cutoff points need to be established locally, taking into consideration the patient material and different interpretation criteria for urine culture. It is also our opinion that these cutoff values need to be verified on a regular basis. Although we did not analyze this in this study, we believe that screening of urine cultures with flow cytometry reduces costs by reducing labor. However, this is a complex issue and has to be evaluated locally.

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